

REMARKS

I. Status of the claims

Claims 38-43 are pending and stand rejected. Applicants acknowledge and thank the Examiner for the indication that "any rejections or objections of record not explicitly addressed herein below, are hereby withdrawn, in light of applicant's arguments, filed June 23, 2009." Final Office Action at 2-3.

II. Rejection Under 35 U.S.C. § 103(a)

Claims 38-43 are rejected under 35 U.S.C. § 103(a) as unpatentable over U.S. Patent No. 6,924,285 ("Himmelsbach"). Final Office Action at 3-4. Applicants respectfully traverse this rejection.

In the Office Action dated May 26, 2009, at page 6, the Office asserted, *inter alia*, that "it is well established that position isomers are structurally prima facie obvious, even in the absence of a teaching to modify." *Id.* (emphasis added). In the Final Office Action, the Office maintained its position, quoting, *inter alia*, M.P.E.P. § 2144.09 (emphasis added):

.... [a]n obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties.

(quoting *In re Payne*, 606 F.2d 303, 313, 203 USPQ 245, 254 (CCPA 1979), and citing *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963); and *In re Dillon*, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1991)). *Id.* at 3-4. Applicants disagree.

"Use of *per se* rules by Office personnel is improper for determining whether claimed subject matter would have been obvious under 35 U.S.C. 103." M.P.E.P.

§ 2144.08(ii) (internal citations omitted). Indeed, the Federal Circuit has clarified the very "per se rule" now relied upon by the Office. In *Takeda Chemical Industries, Ltd., v. AlphaPharm Pty, Ltd.*, 492 F.3d 1350, 83 U.S.P.Q.2d 1353 (BNA) 1169, (Fed. Cir. 2007), the Federal Circuit explained:

[In] *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995), ... we stated that "[n]ormally a prima facie case of obviousness is based upon structural similarity, i.e., an established structural relationship between a prior art compound and the claimed compound." That is so because close or established "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." *Id.* A known compound may suggest its homolog, analog, or isomer because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." *Id.* We clarified, however, that in order to find a prima facie case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required.

(emphasis added) (internal citations omitted).

Accordingly, even in cases where a homolog, an analog, or an isomer of the claimed compound is disclosed in the art, a prima facie case of obviousness requires a showing of motivation to make the claimed compound.

Indeed, following *KSR Int'l Co. v. TeleFlex Inc.*, 127 S.Ct. 1727 (2007), the Federal Circuit has elaborated upon the requirements for establishing a prima facie case of obviousness in cases involving structural similarity.

A requisite "preliminary finding [is] that one of ordinary skill in the art would have selected [the prior art compound] as a lead compound." *The Procter & Gamble Company v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (emphasis added) (citing *Takeda*, 492 F.3d at 1359 and *Eisai Co. Ltd. v. Dr.*

Reddy's Labs., Ltd., 533 F.3d 1353, 1359 (Fed. Cir. 2008) ("post-KSR, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound" in the prior art)).

Once the Office has made that requisite preliminary finding, "it remains necessary to **identify some reason that would have led a chemist to modify a known compound in a particular manner....**" *Procter & Gamble*, 566 F.3d at 994 (emphasis added) (*quoting Takeda*, 492 F.3d at 1357) (explaining that "KSR presupposes that the record up to the time of invention would give some reasons, available within the knowledge of one of skill in the art, to make particular modifications to achieve the claimed compound."); *see also Eisai*, 533 F.3d at 1359.

In other words,

Obviousness based on structural similarity thus can be proved by **identification of some motivation that would have led one of ordinary skill in the art to [1] select and then [2] modify a known compound (i.e. a lead compound) in a particular way** to achieve the claimed compound.

Eisai, 533 F.3d at 1357 (emphasis and parentheticals added) (citing *Takeda*, 492 F.3d at 1356).

A. The Office Has Failed To Make A Reasoned Identification of a Lead Compound

As discussed above, a prima facie case of obviousness preliminarily requires a reasoned identification of a lead compound in the prior art. In the present case, the Office has not provided any reason why one of ordinary skill in the art would have selected Himmelsbach's Example (38) as a lead compound for further modification and thus has not established a prima facie case of obviousness.

Furthermore, one of ordinary skill in the art would have had no reason to select Himmelsbach's Example (38) as a lead compound. Himmelsbach's broadest genus encompasses hundreds of thousands, if not millions, of quinazoline compounds. Himmelsbach discloses sixteen (16) synthetic examples that Himmelsbach teaches can be used to make at least **166** different compounds. See Examples 1-16. In addition, Himmelsbach seemingly prophetically provides the structures of **186** other compounds, one of which is the compound cited in the Office Action. See col. 56, ll. 9-11; col. 56 - col. 128. However, Himmelsbach does not appear to have actually made any of those 186 compounds. Thus, the compound cited by in the Office Action is one of the **352** compounds expressly disclosed in Himmelsbach. Accordingly, that bare disclosure would not have provided one of ordinary skill in the art with a reason to select the compound cited in the Office Action for further modification.

In addition, where a reference discloses a broad generic formula, its "focus[] on" a group of preferred compounds "appears to teach away from the selection of [other compounds within its disclosure]." *In re Baird*, 16 F.3d 380, 382 (Fed. Cir. 1994); see also M.P.E.P. § 2144.08(II)(A)(4)(c). In the present case, Himmelsbach focuses on a group of preferred compounds that does not include Example (38) and thus teaches away from selecting Example (38) as a lead compound.

For example, Himmelsbach discloses two groups of "[p]articularly preferred compounds" (col. 6, l. 28 - col. 7, l. 20, and col. 11, l. 8 - col. 12, l. 12) and a group of "[m]ost particularly preferred compounds" (col. 8, l. 21 - col. 11, l. 7); Example (38) is not one of those. Example (38) also is not one of the 22 "examples of particularly preferred

compounds" independently named in columns 12-13 and expressly claimed in claim 6. And Example (38) is not one of the 27 compounds for which Himmelsbach provides data. Col. 19, l. 50 - col. 20, l. 15. Accordingly, Himmelsbach's focus on preferred compounds that do not include Example (38) would have, in accord with *Baird*, taught away from the selection of Example (38) as a lead compound.

In view of the complete absence from the Office of any reason why one of ordinary skill in the art would have been led to select Example (38) as a lead compound and further in view of the reasons described above why one of ordinary skill in the art would *not* have been led to select it, Applicants submit that a *prima facie* case of obviousness has not been established. Accordingly, Applicants respectfully request withdrawal of this rejection.

B. The Office Also Has Failed to Identify A Reason to Make The Requisite Modification to Example (38)

In addition to presenting a reasoned identification of a lead compound in the prior art, to establish a *prima facie* case of obviousness, the Office must identify some reason that would have led one of ordinary skill in the art to modify that lead compound in the particular manner required to attain the claimed compound. In the present case, the Office has not provided any particular reason why one of ordinary skill in the art would have modified the phenyl ring of Himmelsbach's Example (38) as presently claimed, and thus has not established a *prima facie* case of obviousness.

The Office's conclusion of obviousness relies on the generalization that changing a position isomer of a known compound would have been obvious *for any compound*. But the law expressly rejects that reasoning:

" . . . generalization should be avoided insofar as specific chemical structures are alleged to be *prima facie* obvious . . . "

Takeda, 492 F.3d at 1361 (quoting *In re Grabiak*, 769 F.2d 729, 731 (Fed. Cir. 1985)).

Rather, the differences between the claimed compound and the prior art compound must be considered within the context of the particular compounds. *In re Grabiak*, 769 F.2d at 731 (refusing to find motivation to make a structural change based on a reference "dealing with quite a different part of quite a different molecule.").

The Office's focus on modification of the substituents of a single structural aspect -- the phenyl ring in "R^b" of Himmelsbach's Formula I -- of Himmelsbach's compounds is similarly flawed.

Himmelsbach does not focus on modifying or varying the substituents on phenyl rings in its compounds, let alone on those of the phenyl ring in Example (38). Rather, to the extent that Himmelsbach teaches anything about phenyl ring substituents, it teaches a clear preference for 3-chloro, 4-fluoro substitution, and thus away from the Office's proposed modification of the 3-chloro, 4-fluoro substituted phenyl ring in Example (38) to a 2-fluoro, 3-chloro substituted phenyl ring.

Notably, not one single compound specifically disclosed in Himmelsbach contains any type of substituent at the 2-position of the phenyl ring, let alone a 2-fluoro group. Furthermore, Himmelsbach's "[p]articularly preferred" and "[m]ost particularly preferred" compounds are all 3-, 4-, or 3,4- substituted at the phenyl group. Col. 6, II. 28-37 and col. 8, II. 21-32. Indeed, the phenyl groups in one group of Himmelsbach's "[p]articularly preferred compounds" must either be 3-chloro, 4-fluoro substituted or 3-ethynyl substituted. Col. 11, II. 8-12. Similarly, all of the 22 "[e]xamples of particularly preferred compounds" recited in column 12, line 32 to column 13, line 26 and claimed in

claim 6 as well as all of the 27 compounds for which Himmelsbach provides data at column 19, line 50 to column 20, line 15 are 3-chloro, 4-fluoro substituted. Finally, 144 of the 166 Examples (about 87%) are 3-chloro, 4-fluoro substituted, as are 171 of the 186 structures (about 92%) shown in columns 56-128. Accordingly, Himmelsbach would have led one of ordinary skill in the art away from the Office's proposed modification of the 3-chloro, 4-fluoro substituents on the phenyl ring in Example (38).

Nothing other than hindsight would have led to the selection or the modification of Example (38). However, "impermissible hindsight must be avoided and the legal conclusion must be reached on the basis of the facts gleaned from the prior art."

M.P.E.P. § 2142.

Here, the Office has not proffered any reason why one of ordinary skill in the art would have selected Example (38) out of the hundreds of disclosed compounds as the lead compound. Additionally, the Office has not shown that there would have been any reason to modify the substituents on the phenyl ring of Example (38) out of the numerous possibilities disclosed in Himmelsbach in a manner necessary to arrive at the presently claimed compound. Applicants therefore respectfully request withdrawal of the obviousness rejection.

III. Conclusion

In view of the foregoing remarks, Applicants respectfully request reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge
any additional required fees to Deposit Account 06-0916.

Respectfully submitted,

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